REMARKS

This is in response to the Office Action mailed September 5, 2002. Reconsideration of this application, in view of the above amendments and the following remarks, is respectfully requested. In this response, new claims 31-34, which claim the invention in somewhat different terms, are presented for the first time and claims 9 and 18 are amended.

Claim Rejections Under 35 U.S.C. §112, First Paragraph and Declaration of Deposit

The claims were rejected for lack of enablement for referring to a deposited strain of *Lactobacillus helveticus* (CM4) in the specification. The Examiner indicates that if deposits have been made under the terms of the Budapest Treaty, than an affidavit or declaration by the Applicants, Assignee, or Agent/Attorney of Record (averring that all restrictions imposed by the depositor on the availability to the public will be irrevocably removed upon the granting of a patent) must be submitted to the PTO.

The Examiner's attention is respectfully directed to page 8 of the specification, which refers to (i) the deposit of the CM4 strain with the National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology; (ii) the Deposit No., FERM BP-6060; and (iii) the date of the deposit, August 15, 1997.

To comply with the Examiner's request, Applicants' Agent herein declares that the deposit of CM4 has been made under the Budapest Treaty, in accordance with 37 C.F.R. §1.801-1.809, and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. In support of this declaration, a copy of the receipt of the original deposit from an International Depository

Authority, along with an English translation thereof, is enclosed as Exhibit 1.

Claim Rejections Under 35 U.S.C. §102(b)

Claims 1, 3-7, 9-15, 17 and 18 have been rejected as anticipated by published European Patent Application EP 583 074 ("the EP application"), an abstract to Nakamura et al. ("the Nakamura abstract"), and commonly owned U.S. Patents 5,766,940 to Yamamoto et al. ("the 940 patent"), and 5,695,796 to Yamamoto et al. ("the '796 patent"). The Examiner alleges that these references disclose the claimed fermentation process. The rejection is respectfully traversed.

Claims 1, 3-7, 10-17 have been cancelled by this Amendment. Claims 9 and 18 have been amended and new claims 19-32 have been added. Independent claims 9 and claim 18 are directed to a method of producing whey containing an ACE inhibitor by a method that includes stirring the mixture of milk-containing starting material and lactic acid bacteria while fermenting. New claims 31 and 32 recite a similar process in simplified terms. The references will be discussed with respect to claims 9 and 18-34.

The EP application discloses an angiotensin converting enzyme (ACE) inhibitor that is a 3-amino acid peptide, Val-Pro-Pro, and is produced by "fermenting foodstuff material containing Val-Pro-Pro as a constituent component with lactic acid bacteria." According to the specification, the fermentation process comprises dissolving the peptide-containing foodstuff material in water, mixing in lactic acid bacteria, and cultivating at a temperature between 25-40°C at a neutral pH for a designated time followed by centrifugation and column purification of the supernatant (page 3, lines 36-38). There is no disclosure or suggestion in the application of

stirring the mixture during the fermentation step, much less stirring to separate curd from whey which is what results from stirring during the fermentation step.

The Nakamura abstract discloses a process of producing ACE inhibitory peptides Ile-Pro-Pro and Val-Pro-Pro by fermenting milk beginning with milk powder using a strain of *Lactobacillus helveticus* and yeast. The bacteria and yeast are cultured with the milk at 37°C for 24 hours. There is no mention of stirring during fermentation to separate curd from whey.

The '940 patent discloses a plasmid vector derived from *Lactobacillus helveticus* that can be used to efficiently transform *Lactobacillus helveticus* and other bacterial strains for more effective use in industrial applications. The '940 patent discloses that *Lactobacillus helveticus*, when used to ferment milk, produces milk containing ACE inhibitors. There is no specific disclosure of *any* fermentation processes. Example 1, contrary to the Examiner's interpretation, does not describe a fermentation process but discloses culturing the transformed *Lactobacillus helveticus* under ordinary conditions for plasmid purification. Again, there is no hint that any stirring should be carried out during the fermenting step in the '940 patent to separate curd pieces from whey.

The '796 patent discloses a genetically engineered strain of *Lactobacillus helveticus* which has increased acidity when cultured and results in the production of more ACE inhibitory peptides when fermented in milk. A fermentation process whereby skim milk is cultured with the mutant strain at 37°C for 30 hours. There is no disclosure of stirring during fermentation to separate curd pieces from whey.

To meet the burden of anticipation under 35 U.S.C. §102(b), a single prior art reference must disclose each and every element of the rejected claim(s). See, M.P.E.P. § 2131. "A claim

is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must be literally present, arranged as in the claim. *Perkin Elmer Corp.* 732 F.2d 888, 894, 221 USPQ 669, 673. Here, none of the cited references discloses or suggests stirring during the fermentation step.

Regarding the Examiner's contention that the viscosity of milk is inherent, Applicants respectfully disagree. It is emphatically asserted that the viscosity of whey, which is the resulting liquid produced by the claimed process of the present invention, has a viscosity that is easily distinguishable from milk. Accordingly, the viscosity is not an "inherent" property.

In summary, none of the EP application, the Nakamura abstract the '940 patent and the '796 patent teach a method for producing whey containing an ACE inhibitor which comprises stirring the mixture of milk and lactic acid bacteria and yeast during fermentation. In the present invention, this combined stirring/fermentation step separates curd from the whey (which contains the ACE inhibitory peptides). In fact, none of the above-identified references disclose a fermentation process that requires stirring at any time during the process of producing the ACE inhibitory peptides, much less during the fermentation process. It cannot be assumed by the Examiner, absent explicit disclosure, that the fermentation process described in these references was performed while stirring. By contrast, according to the standard procedures used in the art, and by the references themselves, it can be asserted that no stirring occurred during fermentation. Accordingly, it is respectfully asserted that none of the references anticipate the present claims.

Claims 1, 3-5, 7, 9-13, 15, 17 and 18 also stand rejected as anticipated by the '796 patent and U.S. Patent 5,541,11 to Yamamoto et al., also commonly-owned. The Examiner contends that the references teach the claimed process and that the viscosity of milk is inherent to the milk.

This rejection is respectfully traversed.

As indicated above, Claim 9 and 18 have been amended, and new claims 31-34 have been added to more precisely recite that the method of the present invention requires stirring while fermenting to separate curd from whey.

The '796 patent has been discussed above. The '111 patent teaches mutant strains of lactic acid bacterial of the genus *Lactobacillus* having increased acidity and other characteristics that can be used to ferment milk. A fermentation process that employs static fermentation is described in Example 1 of the '111 patent (bacteria cultured with 9% skim milk at 37° for three days; col. 5, lines 66-67). There is no mention of stirring the mixture during fermentation, much less to separate the curd from the whey, resulting in whey containing ACE inhibitory peptides after separation. Thus, the references do not disclose all the features of claims 1, 18, or 31-34. The requirements for anticipation under 35 U.S.C. §102(b) have been discussed above. It is respectfully asserted that neither the '796 patent nor the '111 patent meet these requirements an that neither reference anticipates the present claims. Accordingly, withdrawal of the rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103

Claims 1, and 3-18 have been rejected as obvious over the EP patent, the Nakamura

abstract or the '940 patent. The Examiner alleges that although none of the references teach *Lactobacillus helveticus* strain CM4 FERM BP-6060, it would have been obvious to substitute such a strain for use in the fermentation process. This rejection is respectfully traversed.

The present claims call for stirring during the fermentation step. This is done to separate the curd pieces from the whey during fermentation. The whey contains the ACE inhibitory peptides. By stirring during fermentation, whey is generated that contains a remarkably high yield of ACE inhibitory peptides compared to the whey prepared by ordinary, static fermentation (*i.e.*, fermenting without stirring) as described by the prior art. The instant specification supports a distinction between the prior art method of static fermentation, and the method of the present invention at page 11, last line, to page 12, line 10. Specifically, the specification states that the prior art static method of fermentation results in a product that is a

> "yogurt-like gel that is substantially contiguous all over the volume of a fermenter tank. Such fermented milk curd cannot be made into a fermented milk of low viscosity...by stirring the curd into pieces after fermentation."

By stirring the mixture during the fermentation step as opposed to after, as understood is done in following the prior art method of static fermentation, the present inventors have unexpectedly increased the yield of whey compared to the prior art method. This in turn has increased the yield of ACE inhibitory peptides produced by the fermentation process. This is demonstrated in Comparative Example 1 and Example 1, beginning on page 15 of the instant specification. Comparative Example 1 describes results of a fermentation process of skim milk with *Lactobacillus helveticus* under static conditions at 34°C for 25 hours. The yogurt-like gel is

then stirred to separate the curd from the whey and lower the viscosity, centrifuged to separate the whey, and column-purified. This process resulted in a product with a viscosity of 415 cp, 25% whey recovery of 2.5 kg, and an ACE inhibitory peptide concentration in the whey of 7.1 mg/100 g of fermented product. In contrast, Example 1, beginning on page 18, describes a fermentation process of skim milk using the methods of the invention, *i.e.*, stirring the mixture at 50 rpm during fermentation to separate the curd from the whey. The fermentation was performed at 34°C for 29 hours. This process resulted in 60% whey recovery (6 kg), a viscosity of 4.5 cp, and recovery of 9.1 mg/100 g of ACE inhibitory peptides (see Table 1 on page 22). Thus, use of the method of the present invention increased the yield of ACE inhibitory peptides by more than 25% compared to static fermentation , *i.e.*, no stirring. This surprising increase is entirely unexpected and is not suggested or disclosed in the prior art of record.

Similar experiments are described in Example 2 and comparative Example 2. In comparative Example 2, which describes a static fermentation process, the viscosity of the fermented yogurt-like gel was very high, 1832 cp, which resulted, after centrifugation, in only 1% whey recovery. By contrast, when the same starting material was fermented during stirring under the same conditions, the mixture containing the separated curd/whey had a viscosity of 8.1 cp, resulting in 64% of whey recovery after centrifugation (see Table 1 on page 22).

To meet the burden of *prima facie* obviousness under 35 U.S.C. §103(a), the Examiner must establish that three criteria have been met. First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach all

of the claimed limitations. Both the motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See, M.P.E.P §2143; citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

None of the above-cited prior art references teach or suggest that the mixture should be stirred during the fermentation process, much less stirring in order to separate curd pieces from the whey during the fermentation process, or a process by which whey is separated from the milk. To the contrary, as indicated in the instant specification on page 3, line 9, to page 4, line 8, the prior art understood that

> Conventional lactic acid fermentation ... is carried out by mixing starter bacteria and a starting material by stirring to form a uniform mixture, and then *fermenting the mixture under static conditions* in order to make the resulting product as a whole in the form of curd. Such static conditions are believed to be required because, when a fermentation liquid is at reduced pH due to fermentative proliferation of lactic acid bacteria, application of vibration, such as by stirring or shaking, to such fermentation liquid will cause whey off and coarse texture of the resulting fermented milk products.

Simply stated, the prior art taught away from stirring during the fermentation step. Instead, the art recommended fermenting under "static" conditions-exactly the opposite of the present invention. Accordingly, it is not expressly stated in, and cannot be assumed from, either the EP patent or the Nakamura abstract, that the fermentation processes described therein involved stirring during fermentation. As indicated above, the '940 patent does not disclose a

fermentation process at all.

There is no teaching or suggestion in the prior art or record to stir during fermentation, much less that making such a modification (contrary to the standard fermentation protocol) will work, unless the objective of one skilled in the art was to "cause whey off and coarse texture" of the fermented milk.

In summary, the art of record does not suggest the method of the claims and the rejection of claims 1 and 3-18 should be withdrawn.

Claims 1 and 3-18 have also been rejected as obvious over the '796 patent or the '111 patent, commonly-owned, in view of the abstract of Japanese Patent 03-120225 ("the JP abstract"), the EP application, the Nakamura abstract or the '940 patent. The Examiner alleges that although none of the references teach *Lactobacillus helveticus* strain CM4 FERM BP-6060, it would have been obvious to substitute such a strain for use in the fermentation process. This rejection is respectfully traversed.

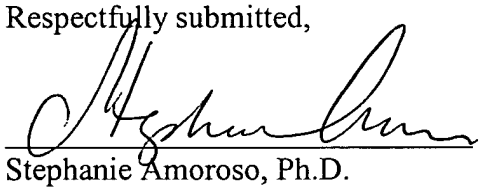
The '796 patent, the '111 patent the EP application, the Nakamura abstract and the '940 patent have been discussed above. The JP abstract discloses 6 novel peptides that have ACE inhibitory activity and a method of preparing such peptides. There is no disclosure of a fermentation process in the abstract. Accordingly, it follows that the JP abstract cannot supply the missing teaching or suggestion to modify the prior art method of static fermentation, or provide the motivation to combine any of the other cited references to do so (which, even if combined , would not lead one of skill in the art to the method of the present invention). In view of the foregoing and the arguments presented above, withdrawal of this rejection is respectfully

requested.

In view of the above amendments and remarks, the subsisting claims are believed to be in condition for allowance and such action is respectfully requested.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Stephanie Amoroso, Ph.D.
Reg. No. 51,401
Agent for Applicants

DARBY & DARBY, P.C.
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700

Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No: 4703/0J586

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXPRESS MAIL CERTIFICATE 294034791US

Date 2/3/03 Label No. EV

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

L. Santini L. Santini

Name (Print) Signature

In re Application of: Shuji KITAMURA; Takashi UEYAMA

Serial No.: 09/889,313 Art Unit: 1651

Confirmation No.: 2308

Filed: July 11, 2001 Examiner: M. Meller

For: PROCESS FOR PRODUCING FERMENTED MILK CONTAINING ANGIOTENSIN CONVERTING ENZYME INHIBITORY PEPTIDE AND PROCESS FOR PRODUCING MILK SERUM

MARK-UP FOR AMENDMENT PURSUANT TO 37 C.F.R. §1.121

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

February 3, 2003

Sir:

IN THE CLAIMS

9. (Twice Amended) A method for producing whey containing an angiotensin converting enzyme inhibitory peptide comprising:

(i) mixing lactic acid bacteria and a starting material containing milk by stirring to prepare a mixed material;

(ii) fermenting said mixed material while stirring so that curd pieces and whey containing an angiotensin converting enzyme inhibitory peptide are generated,

whereby fermented milk containing said curd pieces and said whey containing the angiotensin converting enzyme inhibitory peptide is produced; and

subjecting the fermented milk [produced by the method of claim 1] to at least one of centrifugation and filter processing to separate and recover whey.

18. (Amended) A method for producing whey containing an angiotensin converting inhibitory peptide comprising:

(i) mixing lactic acid bacteria and a starting material containing material containing milk by stirring to prepare a mixed material;

(ii) fermenting said mixed material while stirring so that curd pieces and whey containing an angiotensin converting enzyme inhibitory peptide are generated

(iii) fermenting said mixed material under static conditions,

whereby fermented milk containing said curd pieces and said whey containing the angiotensin converting enzyme inhibitory peptide is produced; and

subjecting the fermented milk [produced by the method of claim 10] to at least one of centrifugation and filter pressing to separate and recover whey.